CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074700

Trade Name : BUMETANIDE TABLETS USP

Generic Name: Bumetanide Tablets USP

Sponsor : Eon Labs Manufacturing, Inc.

Approval Date: November 21, 1996

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074700

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074700

APPROVAL LETTER

ANDA 74-700

11/21/96

Eon Labs Manufacturing, Inc.
Attention: Sadie M. Ciganek
227-15 N. Conduit Ave.
Laurelton, N.Y. 11413

Dear Madam:

This is in reference to your abbreviated new drug application dated June 15, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Bumetanide Tablets USP, 0.5 mg, 1 mg and 2 mg.

Reference is also made to your amendments dated September 3, and October 16, 1996.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Bumetanide Tablets USP, 0.5 mg, 1 mg and 2 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Bumex® Tablets 0.5 mg, 1 mg and 2 mg, respectively, of Hoffmann-LaRoche, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/ 11/21/96

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 74-700
Dup File
Division File
Field Copy
HFD-600/Reading File

Endorsements:

HFD-625/SSherken/10/29/96
HFD-625/MSmela/10/29/96
HFD-617/SO'Keefe/10/30/96
HFD-613/JGrace/10/31/96
HFD-620/ARudman
HFD-613/CHolquist/10/31/96
X:\NEW\FIRMSAM\EON\LTRS&RE
F/t by: gp/11/1/96
APPROVED

/S/

/S/ 11/4/96

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074700

FINAL PRINTED LABELING

NDC 0185-0128-01

Lot No.:
Exp. Date:

USUAL DOSAGE: See accompanying literature for complete prescribing information.

Store at controlled room temperature 15° - 30°C (59° - 86°F).

Preserve in a tight, light-resistant container as defined in the USP. Dispense contents with a child-resistant closure as required.

Issued 2/96

Bumetanide Tablets, USP

0.5 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 Tablets

Eon Labs

Each tablet contains:
Bumetanide, USP . . . 0.5 mg

KEEP TIGHTLY CLOSED.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

3 0185-0128-01 3

NDC 0185-0128-05

Lot No.:
Exp. Date:

USUAL DOSAGE: See accompanying literature for complete prescribing information.

Store at controlled room temperature 15° - 30°C (59° - 86°F).

This is a bulk package. Dispense contents with a child-resistant closure (as required) and in a tight, light-resistant container as defined in the USP.

Issued 2/96

Bumetanide Tablets, USP

0.5 mg

CAUTION: Federal law prohibits dispensing without prescription.

500 Tablets

Eon Labs

Each tablet contains:
Bumetanide, USP . . . 0.5 mg

KEEP TIGHTLY CLOSED.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

3 0185-0128-05 1

NDC 0185-0129-01

Lot No.:
Exp. Date:

USUAL DOSAGE: See accompanying literature for complete prescribing information.

Store at controlled room temperature 15° - 30°C (59° - 86°F).

Preserve in a tight, light-resistant container as defined in the USP. Dispense contents with a child-resistant closure as required.

Issued 2/96

Bumetanide Tablets, USP

1 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 Tablets

Eon Labs

Each tablet contains:
Bumetanide, USP . . . 1 mg

KEEP TIGHTLY CLOSED.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

3 0185-0129-01 0

NDC 0185-0129-05

Lot No.:
Exp. Date:

USUAL DOSAGE: See accompanying literature for complete prescribing information.

Store at controlled room temperature 15° - 30°C (59° - 86°F).

This is a bulk package. Dispense contents with a child-resistant closure (as required) and in a tight, light-resistant container as defined in the USP.

Issued 2/96

Bumetanide Tablets, USP

1 mg

CAUTION: Federal law prohibits dispensing without prescription.

500 Tablets

Eon Labs

Each tablet contains:
Bumetanide, USP . . . 1 mg

KEEP TIGHTLY CLOSED.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

3 0185-0129-05 8

BUMETANIDE
TABLETS, USP

0128

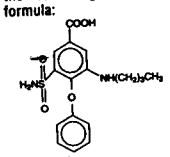
BUMETANIDE TABLETS, USP

WARNING: Bumetanide is a potent diuretic which, if given in excessive amounts, can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required, and dose and dosage schedule have to be adjusted to the individual patient's needs. (See **DOSAGE AND ADMINISTRATION.**)

DESCRIPTION:

Bumetanide is a loop diuretic, available as scored tablets. Each tablet for oral administration contains 0.5 mg, 1 mg or 2 mg of bumetanide. In addition, each tablet contains the following inactive ingredients: anhydrous lactose, corn starch, magnesium stearate, microcrystalline cellulose, pregelatinized starch, talc, with the following dye systems: 0.5 mg- D&C Yellow No. 10 Aluminum Lake, FD&C Blue No. 1 Aluminum Lake and FD&C Red No. 40 Aluminum Lake; 1 mg- D&C Yellow No. 10 Aluminum Lake; 2 mg- synthetic black iron oxide, synthetic red iron oxide and synthetic yellow iron oxide.

Chemically, bumetanide is 3-(butylamino)-4-phenoxy-5-sulfamoylbenzoic acid. It is a practically white powder having a calculated molecular weight of 364.42, and the following structural formula:



$C_{17}H_{20}N_2O_5S$

CLINICAL PHARMACOLOGY:

Bumetanide is a loop diuretic with a rapid onset and short duration of action. Pharmacological and clinical studies have shown that 1 mg bumetanide has a diuretic potency equivalent to approximately 40 mg furosemide. The major site of bumetanide action is the ascending limb of the loop of Henle.

The mode of action has been determined through various clearance studies in both humans and experimental animals. Bumetanide inhibits sodium reabsorption in the ascending limb of the loop of Henle, as shown by marked reduction of free-water clearance ($^{C}H_2O$) during hydration and tubular free-water reabsorption ($T^{C}H_2O$) during hydropenia. Reabsorption of chloride in the ascending limb is also blocked by bumetanide, and bumetanide is somewhat more chloruretic

of Henle.

The mode of action has been determined through various clearance studies in both humans and experimental animals. Bumetanide inhibits sodium reabsorption in the ascending limb of the loop of Henle, as shown by marked reduction of free-water clearance (C^{H_2O}) during hydration and tubular free-water reabsorption ($T^{C}H_2O$) during hydropenia. Reabsorption of chloride in the ascending limb is also blocked by bumetanide, and bumetanide is somewhat more chioruretic than natriuretic.

Potassium excretion is also increased by bumetanide, in a dose-related fashion.

Bumetanide may have an additional action in the proximal tubule. Since phosphate reabsorption takes place largely in the proximal tubule, phosphaturia during bumetanide-induced diuresis is indicative of this additional action. This is further supported by the reduction in the renal clearance of bumetanide by probenecid, associated with diminution in the natriuretic response. This proximal tubular activity does not seem to be related to an inhibition of carbonic anhydrase. Bumetanide does not appear to have a noticeable action on the distal tubule.

Bumetanide decreases uric acid excretion and increases serum uric acid. Following oral administration of bumetanide the onset of diuresis occurs in 30 to 60 minutes. Peak activity is reached between 1 and 2 hours. At usual doses (1 to 2 mg) diuresis is largely complete within 4 hours; with higher doses, the diuretic action lasts for 4 to 6 hours.

Several pharmacokinetic studies have shown that bumetanide, administered orally or parenterally, is eliminated rapidly in humans, with a half-life of between 1 and 1¼ hours. Plasma protein-binding is in the range of 94% to 96%.

Oral administration of carbon-14 labeled bumetanide to human volunteers revealed that 81% of the administered radioactivity was excreted in the urine, 45% of it as unchanged drug. Urinary and biliary metabolites identified in this study were formed by oxidation of the N-butyl side chain. Biliary excretion of bumetanide amounted to only 2% of the administered dose.

INDICATIONS AND USAGE:

Bumetanide tablets are indicated for the treatment of edema associated with congestive heart failure, hepatic and renal disease, including the nephrotic syndrome.

Almost equal diuretic response occurs after oral and parenteral administration of bumetanide. Therefore, if impaired gastrointestinal absorption is suspected or oral administration is not practical, bumetanide should be given by the intramuscular or intravenous route.

Successful treatment with bumetanide following instances of allergic reactions to furosemide suggests a lack of crosssensitivity.

CONTRAINDICATIONS:

Bumetanide is contraindicated in anuria. Although bumetanide can be used to induce diuresis in renal insufficiency, any marked increase in blood urea nitrogen or creatinine, or the development of oliguria during therapy of patients with progressive renal disease, is an indication for discontinuation of treatment with bumetanide. Bumetanide is also contraindicated in patients in hepatic coma or in states of severe electrolyte depletion until the condition is improved or corrected. Bumetanide is contraindicated in patients hypersensitive to this drug.

WARNINGS:

1. Volume and electrolyte depletion. The dose of bu-

cated in patients hypersensitive to this drug.

WARNINGS:

1. Volume and electrolyte depletion. The dose of bumetanide should be adjusted to the patient's need. Excessive doses or too frequent administration can lead to profound water loss, electrolyte depletion, dehydration, reduction in blood volume and circulatory collapse with the possibility of vascular thrombosis and embolism, particularly in elderly patients.

2. Hypokalemia. Hypokalemia can occur as a consequence of bumetanide administration. Prevention of hypokalemia requires particular attention in the following conditions: patients receiving digitalis and diuretics for congestive heart failure, hepatic cirrhosis and ascites, states of aldosterone excess with normal renal function, potassium-losing nephropathy, certain diarrheal states, or other states where hypokalemia is thought to represent particular added risks to the patient, i.e., history of ventricular arrhythmias.

In patients with hepatic cirrhosis and ascites, sudden alterations of electrolyte balance may precipitate hepatic encephalopathy and coma. Treatment in such patients is best initiated in the hospital with small doses and careful monitoring of the patient's clinical status and electrolyte balance. Supplemental potassium and/or spironolactone may prevent hypokalemia and metabolic alkalosis in these patients.

3. Ototoxicity. In cats, dogs and guinea pigs, bumetanide has been shown to produce ototoxicity. In these test animals bumetanide was 5 to 6 times more potent than furosemide and, since the diuretic potency of bumetanide is about 40 to 60 times furosemide, it is anticipated that blood levels necessary to produce ototoxicity will rarely be achieved. The potential exists, however, and must be considered a risk of intravenous therapy, especially at high doses, repeated frequently in the face of renal excretory function impairment. Potentiation of aminoglycoside ototoxicity has not been tested for bumetanide. Like other members of this class of diuretics, bumetanide probably shares this risk.

4. Allergy to sulfonamides. Patients allergic to sulfonamides may show hypersensitivity to bumetanide.

5. Thrombocytopenia. Since there have been rare spontaneous reports of thrombocytopenia from postmarketing experience, patients should be observed regularly for possible occurrence of thrombocytopenia.

PRECAUTIONS:

General: Serum potassium should be measured periodically and potassium supplements or potassium-sparing diuretics added if necessary. Periodic determinations of other electrolytes are advised in patients treated with high doses or for prolonged periods, particularly in those on low salt diets.

Hyperuricemia may occur; it has been asymptomatic in cases reported to date. Reversible elevations of the BUN and creatinine may also occur, especially in association with dehydration and particularly in patients with renal insufficiency. Bumetanide may increase urinary calcium excretion with resultant hypocalcemia.

Diuretics have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Laboratory Tests: Studies in normal subjects receiving bumetanide revealed no adverse effects on glucose tolerance, plasma insulin, glucagon and growth hormone levels, but the possibility of an effect on glucose [illegible] exists. Periodic

odically and potassium supplements or potassium-sparing diuretics added if necessary. Periodic determinations of other electrolytes are advised in patients treated with high doses or for prolonged periods, particularly in those on low salt diets.

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Laboratory Tests: Studies in normal subjects receiving bumetanide revealed no adverse effects on glucose tolerance, plasma insulin, glucagon and growth hormone levels, but the possibility of an effect on glucose metabolism exists. Periodic determinations of blood sugar should be done, particularly in patients with diabetes or suspected latent diabetes.

Patients under treatment should be observed regularly for possible occurrence of blood dyscrasias, liver damage or idiosyncratic reactions, which have been reported occasionally in foreign marketing experience. The relationship of these occurrences to bumetanide use is not certain.

Drug Interactions:

1. Drugs with ototoxic potential (See **WARNINGS**): Especially in the presence of impaired renal function, the use of parenterally administered bumetanide in patients to whom aminoglycoside antibiotics are also being given should be avoided, except in life-threatening conditions.

2. Drugs with nephrotoxic potential: There has been no experience on the concurrent use of bumetanide with drugs known to have a nephrotoxic potential. Therefore, the simultaneous administration of these drugs should be avoided.

3. Lithium: Lithium should generally not be given with diuretics (such as bumetanide) because they reduce its renal clearance and add a high risk of lithium toxicity.

4. Probenecid: Pretreatment with probenecid reduces both the natriuresis and hyperreninemia produced by bumetanide. This antagonistic effect of probenecid on bumetanide natriuresis is not due to a direct action on sodium excretion but is probably secondary to its inhibitory effect on renal tubular secretion of bumetanide. Thus, probenecid should not be administered concurrently with bumetanide.

5. Indomethacin: Indomethacin blunts the increases in urine volume and sodium excretion seen during bumetanide treatment and inhibits the bumetanide-induced increase in plasma

renin activity. Concurrent therapy with bumetanide is thus not recommended.

6. Antihypertensives: Bumetanide may potentiate the effect of various antihypertensive drugs, necessitating a reduction in the dosage of these drugs.

7. Digoxin: Interaction studies in humans have shown no effect on digoxin blood levels.

8. Anticoagulants: Interaction studies in humans have shown bumetanide to have no effect on warfarin metabolism or on plasma prothrombin activity.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Bumetanide was devoid of mutagenic activity in various strains of *Salmonella typhimurium* when tested in the presence or absence of an *in vitro* metabolic activation system. An 18-month study showed an increase in mammary adenomas of questionable significance in female rats receiving oral doses of 60 mg/kg/day (2000 times a 2-mg human dose). A repeat study at the same doses failed to duplicate this finding.

Reproduction studies were performed to evaluate general reproductive performance and fertility in rats at oral dose levels of 10, 30, 60 or 100 mg/kg/day. The pregnancy rate was slightly decreased in the treated animals; however, the differences were small and not statistically significant.

Pregnancy: Teratogenic Effects: Pregnancy Category C. Bumetanide is neither teratogenic nor embryocidal in mice when given in doses up to 3.4 times the maximum human therapeutic dose.

Bumetanide has been shown to be nonteratogenic, but it has a slight embryocidal effect in rats when given in doses of 3400 times the maximum human therapeutic dose and in rabbits at doses of 3.4 times the maximum human therapeutic dose. In one study, moderate growth retardation and increased incidence of delayed ossification of sternebrae were observed in rats at oral doses 100 mg/kg/day, 3400 times the maximum human therapeutic dose. These effects were associated with maternal weight reductions noted during dosing. No such adverse effects were observed at 30 mg/kg/day (1000 times the maximum human therapeutic dose). No fetotoxicity was observed at 1000 to 2000 times the human therapeutic dose.

In rabbits, a dose-related decrease in litter size and an increase in resorption rate were noted at oral doses of 0.1 and 0.3 mg/kg/day (3.4 and 10 times the maximum human therapeutic dose). A slightly increased incidence of delayed ossification of sternebrae occurred at 0.3 mg/kg/day; however, no such adverse effects were observed at the dose of 0.03 mg/kg/day. The sensitivity of the rabbit to bumetanide parallels the marked pharmacologic and toxicologic effects of the drug in this species.

Bumetanide was not teratogenic in the hamster at an oral dose of 0.5 mg/kg/day (17 times the maximum human therapeutic dose). Bumetanide was not teratogenic when given intravenously to mice and rats at doses up to 140 times the maximum human therapeutic dose.

There are no adequate and well-controlled studies in pregnant women. A small investigational experience in the United States and marketing experience in other countries to date have not indicated any evidence of adverse effects on the fetus, but these data do not rule out the possibility of harmful effects. Bumetanide should be given to a pregnant woman only if the potential benefit justifies the

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Nursing Mothers: It is not known whether this drug is excreted in human milk. As a general rule, nursing should not be undertaken while the patient is on bumetanide since it may be excreted in human milk.

Pediatric Use: Safety and effectiveness in pediatric patients below the age of 18 have not been established.

ADVERSE REACTIONS:

The most frequent clinical adverse reactions considered probably or possibly related to bumetanide are muscle cramps (seen in 1.1% of treated patients), dizziness (1.1%), hypotension (0.8%), headache (0.6%), nausea (0.6%), and encephalopathy (in patients with preexisting liver disease) (0.6%). One or more of these adverse reactions have been reported in approximately 4.1% of bumetanide-treated patients.

Less frequent clinical adverse reactions to bumetanide are impaired hearing (0.5%), pruritus (0.4%), electrocardiogram changes (0.4%), weakness (0.2%), hives (0.2%), abdominal pain (0.2%), arthritic pain (0.2%), musculoskeletal pain (0.2%), rash (0.2%) and vomiting (0.2%). One or more of these adverse reactions have been reported in approximately 2.9% of bumetanide-treated patients.

Other clinical adverse reactions, which have each occurred in approximately 0.1% of patients, are vertigo, chest pain, ear discomfort, fatigue, dehydration, sweating, hyperventilation, dry mouth, upset stomach, renal failure, asterixis, itching, nipple tenderness, diarrhea, premature ejaculation and difficulty maintaining an erection.

Laboratory abnormalities reported have included hyperuricemia (in 18.4% of patients tested), hypochloremia (14.9%), hypokalemia (14.7%), azotemia (10.6%), hyponatremia (9.2%), increased serum creatinine (7.4%), hyperglycemia (6.6%), and variations in phosphorus (4.5%), CO_2 content (4.3%), bicarbonate (3.1%) and calcium (2.4%). Although manifestations of the pharmacologic action of bumetanide, these conditions may become more pronounced by intensive therapy.

Also reported have been thrombocytopenia (0.2%) and deviations in hemoglobin (0.8%), prothrombin time (0.8%), hematocrit (0.6%), WBC (0.3%) and differential counts (0.1%). There have been rare spontaneous reports of thrombocytopenia from postmarketing experience.

Diuresis induced by bumetanide may also rarely be accompanied by changes in LDH (1.0%), total serum bilirubin (0.8%), serum proteins (0.7%), SGOT (0.6%), SGPT (0.5%), alkaline phosphatase (0.4%), cholesterol

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Diuresis induced by bumetanide may also rarely be accompanied by changes in LDH (1.0%), total serum bilirubin (0.8%), serum proteins (0.7%), SGOT (0.6%), SGPT (0.5%), alkaline phosphatase (0.4%), cholesterol (0.4%) and creatinine clearance (0.3%). Increases in urinary glucose (0.7%) and urinary protein (0.3%) have also been seen.

OVERDOSAGE:

Overdosage can lead to acute profound water loss, volume and electrolyte depletion, dehydration, reduction of blood volume and circulatory collapse with a possibility of vascular thrombosis and embolism. Electrolyte depletion may be manifested by weakness, dizziness, mental confusion, anorexia, lethargy, vomiting and cramps. Treatment consists of replacement of fluid and electrolyte losses by careful monitoring of the urine and electrolyte output and serum electrolyte levels.

DOSAGE AND ADMINISTRATION:

Dosage should be individualized with careful monitoring of patient response.

Oral Administration: The usual total daily dosage of bumetanide is 0.5 to 2 mg and in most patients is given as a single dose.

If the diuretic response to an initial dose of bumetanide is not adequate, in view of its rapid onset and short duration of action, a second or third dose may be given at 4 to 5 hour intervals up to a maximum daily dose of 10 mg. An intermittent dose schedule, whereby bumetanide is given on alternate days or for 3 to 4 days with rest periods of 1 to 2 days in between, is recommended as the safest and most effective method for the continued control of edema. In patients with hepatic failure, the dosage should be kept to a minimum, and if necessary, dosage increased very carefully.

Because cross-sensitivity with furosemide has rarely been observed, bumetanide can be substituted at approximately a 1:40 ratio of bumetanide to furosemide in patients allergic to furosemide.

Parenteral Administration: Bumetanide injection may be administered parenterally (IV or IM) to patients in whom gastrointestinal absorption may be impaired or in whom oral administration is not practical.

Parenteral treatment should be terminated and oral treatment instituted as soon as possible.

HOW SUPPLIED:

Bumetanide Tablets, USP are supplied in bottles of 100 and 500 as:

Treatment consists of replacement of fluid and electrolyte losses by careful monitoring of the urine and electrolyte output and serum electrolyte levels.

DOSAGE AND ADMINISTRATION:

Dosage should be individualized with careful monitoring of patient response.

Oral Administration: The usual total daily dosage of bumetanide is 0.5 to 2 mg and in most patients is given as a single dose.

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Parenteral treatment should be terminated and oral treatment instituted as soon as possible.

HOW SUPPLIED:

Bumetanide Tablets, USP are supplied in bottles of 100 and 500 as:

0.5 mg tablets, green-round, bisected; imprinted E 128

1 mg tablets, yellow-round, bisected, imprinted E 129

2 mg tablets, beige to light brown-round, bisected; imprinted E 130

Storage: Store at controlled room temperature 15°-30°C (59°-86°F). Preserve in tight, light-resistant containers as defined in the USP.

Caution: Federal law prohibits dispensing without prescription.

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

Issued 8/96
MF0128ISS0896

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074700

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO #3

2. ANDA 74-700

3. NAME AND ADDRESS OF APPLICANT

Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

4. LEGAL BASIS FOR SUBMISSION

505 (j). No effective patents or exclusivity for NDA 18-255 (Bumex® Tablets - Roche Labs).

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Bumetanide Tablets USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

DOA 6/15/95; Bio Amendment 9/7/95; Bio NA 1/18/96; Chem (Major) NA 1/29/96; Bio ONC 2/21/96; Bio Accept letter 5/23/96; Amend (Major) 3/22/96; NA Chem & Label 8/14/96; Amend (Minor) 9/3/96;* Tel Amend 10/16/96*

* Reviewed amendments

10. PHARMACOLOGICAL CATEGORY

Diuretic

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

(b)4 - Confidential Business

13. DOSAGE FORM

14. POTENCY

Green, round, bisected tablets Imprinted with "E" & "128."	0.5 mg
Yellow, round bisected tablets Imprinted with "E" & "129."	1 mg
Beige to light brown, round, bisected tablets imprinted with "E" & "130."	2 mg

15. CHEMICAL NAME AND STRUCTURE

See review #1.

16. RECORDS AND REPORTS

N/A

17. COMMENTS

Chemistry: Two minor deficiencies remained, after a review of the September 3, 1996 amendment. Both deficiencies were discussed with Eon, in three telephone calls between Eon's representatives, Ms. Ciganek and Dr. Bhfplfgharyya and us. The calls occured on 10/11/96, 10/15/96 and 10/16/96 respectively (see tel-memos in Vol 2.1). On 10/16/96 Eon sent us a telephone amendment to answer our questions by FAX, followed by a hard copy to the ANDA. It was received on 10/21/96.

1. The first deficiency involved setting a specification for residual [redacted] (b)4 - [redacted]. It is used as a solvent during the wet [redacted]

In our telephone call on 10/16/96 we told Eon the we were willing to accept the initial draft ICH's toxicological specification of [redacted] The current ICH draft is even more lenient. Using the respective tablet weight for each dosage strength, and a maximum allowable intake of [redacted] of Bumetanide (as printed on labeling) Eon established specifications of NMT [redacted] for the 0.5 mg tablet, NMT [redacted] for the 1 mg tablet and NMT [redacted] for the 2 mg tablet, which calculates to [redacted] for [redacted] (Note: a possible typo was included for the 2 mg tablet on the cover letter. It lists the specification as [redacted] The specification listed on each of Eon's QC Finished Tablet Specification & Report Forms is [redacted] ppm.

(b)4 - Confidential Business

Eon submitted revised copies of their "Quality Control Finished Tablet Specification & Report Forms for the 0.5 mg, 1 mg and 2 mg tablets. The specification for [redacted] on all three report forms

specification for [redacted]" In addition Eon also included it on their Protocol: B001QC, which includes a description of each test and its specification, for process validation samples, in-process production batches, release specification and full descriptions of all methods used by Eon for this product. Protocol B001QC is satisfactory.

Deficiency #1 in the telephone amendment is satisfactory.

2. The second deficiency involved the in-process testing protocol for friability.

Eon has agreed to conduct friability of the finished dosage forms at the start, middle and end of each compression run during the validation stage of production, then reduce the testing to one test at the beginning of each compression run thereafter. Eon's commitment is satisfactory.

Deficiency #2 in the telephone amendment is satisfactory.

Chemistry is now satisfactory.

DMF [redacted] was found adequate on 7/31/96.

Labeling found adequate on 9/13/96.

BIO found acceptable on 5/23/96.

EER found acceptable 3/29/96.

18. CONCLUSIONS AND RECOMMENDATIONS

Approve ANDA 74-700 - Bumetanide Tablets USP, 0.5 mg, 1 mg & 2 mg.

19. REVIEWER: DATE COMPLETED:

Stephen Sherken October 28, 1996

cc: ANDA 74-700
Division File
Field Copy

Endorsements:
HFD-625/SSherken/10/29/96
HFD-625/MSmela/10/29/96
X:\NEW\FIRMSAM\EON\LTRS&REV\74700.RV3
F/t by: gp/11/1/96

[redacted] /S/ 11/5/96

[redacted] /S/

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074700

BIOEQUIVALENCE REVIEW(S)

D. J

ANDA 74-700

JAN 1 3 1996

Eon Laboratories, Inc.
Attention: Edward Shinal, Ph.D.
227-15 Conduit Ave.,
Laurelton, NY 11413

Dear Dr. Shinal:

Reference is made to the Abbreviated New Drug Application and the amendment submitted on June 15, and September 7, 1995 for Bumetamide Tablets USP, 2.0 mg, 1.0 mg, 0.5 mg.

The Office of Generic Drugs has reviewed the bioequivalence data submitted and the following comments are provided for your consideration:

1. Analytical method SOP #2283 has been submitted in an incomplete form. A complete description of the analytical method, including the complete text of SOP #2283, must be submitted to the application as a condition of approval.

2. In the assay validation section of the bioequivalence study, there is no data to support the stability of the samples and standards under the frozen storage conditions used in the studies for the 82-day period between sample collection (12/10/94) and assay completion (3/2/95). Please submit these data for review.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Jason A. Gross, Pharm.D., at (301) 594-2290. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

(b)4 - Confidential Business

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

D.J

DEC 28 1995

Bumetamide Tablets
Tablets, 2.0 mg, 1.0 mg, 0.5 mg
ANDA #74-700
Reviewer: L.A. Ouderkirk
WP #74700sdw.695

Eon Labs Manufacturing
Laurelton, New York
Submission Dates:
June 15, 1995
September 7, 1995

Review of an In-Vivo Bioequivalence Study, Dissolution Data and a Waiver Request

BACKGROUND:

Bumetanide is a potent diuretic indicated for the treatment of edema associated with congestive heart failure and hepatic and renal disease, including nephrotic syndrome. Bumetanide is contraindicated in anuria, hepatic coma, states of severe electrolyte depletion, and in patients hypersensitive to the drug. The recommended dose ranges generally from 0.5-2.0 mg per day.

Bumetanide is reported to be readily absorbed from the gastrointestinal tract with a Tmax of 0.5-2 hours and a bioavailability of about 80-90%. When administered orally, it is eliminated rapidly with a half-life of between 1 and 2 hours. Oral administration of bumetanide results in 36-60% recovery of the unchanged drug from urine. Following oral administration of the drug, the onset of diuresis occurs in about 30 to 60 minutes. Peak activity is reached between 0.5 and 3 hours. Plasma protein-binding is about 95%. The major site of action of bumetanide is the ascending limb of the Loop of Henle where it inhibits the sodium-potassium-2 chloride absorptive pump.

Bumetanide tablets are marketed by Roche Laboratories as Bumex® tablets, 2 mg, 1 mg and 0.5 mg. The 2 mg strength has been designated as the listed reference product by the Office of Generic Drugs.

I. FASTING IN-VIVO BIOEQUIVALENCE STUDY #930851:

A. STUDY INVESTIGATORS AND CONTRACT LABORATORY:

The bioequivalence study was conducted [redacted]

(b)4 - Confidential Business

B. INFORMED CONSENT AND IRB APPROVAL:

Subjects gave written, informed consent before their acceptance into the study. The study protocol was reviewed and approved by an IRB before its initiation.

C. **STUDY OBJECTIVE:**

The objective of the study was to compare the rate and extent of absorption of the test versus the reference formulation to determine if the test and reference products were bioequivalent.

D. **STUDY DESIGN:**

The study was designed as a random, two-period, two-treatment, two-sequence crossover using 24 healthy male subjects.

E. **SUBJECT SELECTION CRITERIA:**

Subjects selected for the study met the following acceptance criteria:

1. Aged 18-45 years.
2. Healthy, as determined by physical examination, medical history and clinical laboratory diagnostic tests (blood chemistry, hematology, urinalysis).
3. No concurrent illness, acute or chronic diseases or history of serious cardiovascular, pulmonary, renal, G.I., hepatic, or hematologic, endocrine, immunologic, dermatologic, neurologic, or psychiatric disease.
4. No alcohol or drug abuse within the past year.
5. No allergy to bumetanide or sulfonamides.
6. Sitting blood pressure $\geq$ 100/60 mm Hg.
7. No participation in other clinical trials within 28 days of the start of the study.
8. Weight at least 60 kg (132 lb) and within 15% of ideal for height (Metropolitan Life Insurance Company Bulletin, 1983).

F. **SUBJECT RESTRICTIONS:**

1. No alcohol or xanthine consumption beginning 24 hours before dosing and throughout the period of sample collection.
2. No concurrent medication of any type.
3. No Rx drugs beginning two weeks before the study and no OTC drugs (except vitamin supplements) beginning one week before the study.
4. Controlled diet during the study; no other food permitted.
5. Restrictions on recent blood donations as appropriate and other appropriate restrictions.

G. **STUDY SCHEDULES:**

Subjects were fasted overnight before dosing. The volunteers were randomly numbered and divided into two dosing

groups of equal number. A 1 x 2.0 mg oral dose of the test or reference product was administered with 240 ml of water in order of subject number. Subjects continued to fast for four hours post-dose, when a standard lunch was served. To increase urine output, subjects were required to drink 240 mL of water one hour before dosing and at 1, 2, 4, 6, 8, and 10 hours after dosing. No additional water was permitted from one hour before until four hours after dosing.

Venous blood samples (1 x 7 mL) were drawn pre-dose (0 hours) and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 8, and 12 hours post-dose. Plasma was separated by refrigerated centrifugation and was stored frozen pending assay. Urine was collected before dosing and at 0-1, 1-2, 2-4, 4-6, 6-8, 8-10, and 10-12 hours after dosing for possible assay if needed. The blood and urine samples were collected and processed under conditions which minimized their exposure to UV light. A one week washout period was observed between Phase 1 and 2 dosing.

Subjects remained seated for the first two hours after dosing and were either sitting or ambulatory for two hours thereafter. To monitor safety, blood pressure and sitting pulse measurements were obtained pre-dose, and at 2, 5, and 8 hours post-dose. These data were recorded and included in the final study report (Vol. 1.2, pp. 301-326). No clinical or statistical evaluation of these data was reported.

H. DRUG TREATMENTS:

1. **Test Product A:** Bumetanide tablets, 2 mg, (Eon), Lot #941102, Assayed Potency = 99.5%, Units Packaged = (b)4 - (No expiration date given).

2. **Reference Product B:** Bumex® tablets, 2 mg, (Roche), Lot #0310, Assayed Potency = 104.2%, Expiration Date = 12/1/95.

I. ASSAY VALIDATION:

(b)4 - Confidential Business

J. ASSAY NOTES:

(b)4 - Confidential Business

(b)4 - Confidential Business

K. **STATISTICAL ANALYSIS:**

The study data were analyzed by ANOVA and the F-test to determine statistically significant differences between treatments, dosing sequence, subjects within sequence, period, and drug treatment for areas under the curve (AUC), maximum plasma drug levels (Cmax), time to maximum drug levels (Tmax), elimination constants (Kel) and half-life values ($T_{1/2}$). The 90% confidence interval (two one-sided tests procedure) was performed using the ln-transformed values for AUC and Cmax. ANOVA was performed for subject plasma drug concentrations at each sampling time and included all sums of squares (Types I-IV). The ESTIMATE option of SAS GLM was used to generate linear estimates of adjusted treatment mean differences.

L. **CLINICAL NOTES:**

Study Phase 1 and 2 dosing was conducted on 12/10/94 and 12/17/94, respectively. The study subjects were Caucasian males between the ages of 18 and 40 years. Of the 26 subjects who began the study (24 regular subjects and 2 alternates), 25 completed both Phases. Subject #23 was withdrawn by the Medical Designate 1.2 hours before dosing in Period 2, due to medical events. Data from Subjects #1-22, #24, and #25 were included in the statistical analysis, to give a total of 24 data sets, as specified by the study protocol. The randomization scheme was balanced, with 12 subjects receiving each drug treatment in each study period. All blood samples from those subjects completing the study were taken within 2 minutes of the scheduled time.

A total of 10 adverse medical events were experienced by 7 subjects during the study. Six events were experienced after administration of the test product and four after administration of the reference product. Seven of the events were judged to be probably related to the study medications and three were judged

possibly related. All of the events were mild or moderate in intensity and are summarized in **Table** 3, below.

M. RESULTS OF BIOEQUIVALENCE STUDY:

The mean plasma versus time data for the test and reference products for 24 subjects are summarized in **Table 4** and represented graphically in **Figure 1**. Pharmacokinetic summaries of the arithmethic and least-squares mean study results are summarized in **Tables 5 and 6**, respectively. Least-squares means for ln-transformed AUCT, AUCI, and Cmax for the test product were 8.8%, 8.3%, and 9.6% lower, respectively, than were those for the reference. The 90% confidence intervals for ln-transformed AUC(T), AUC(I) and Cmax were within the 80 - 125% range indicating bioequivalence. No statistically significant sequence effects were found for these parameters. Estimated intrasubject CV% calculated for ln-transformed AUC(T), AUC(I) and Cmax was 14.9%, 14.6%, and 18.8%, respectively.

The firm also calculated the 90% confidence intervals for ln-transformed AUC(T), AUC(I) and Cmax using 22 subject data (excluding subjects #3 and #4 who had pre-dose levels of bumetanide, though below the level of assay sensitivity). The confidence intervals were very similar to those reported for the 24 subject data and were still within the 80-125% range indicating bioequivalence.

II. IN-VITRO DISSOLUTION TESTING RESULTS:

The firm conducted dissolution testing on its 2 mg, 1 mg, and 0.5 mg strengths of the test product versus the identical strengths of the reference Bumex® tablets. The results of the dissolution testing and the method used are given in **Table** 7.

III. REQUEST FOR WAIVER OF IN-VIVO BIOEQUIVALENCE:

The firm has requested waiver of the in-vivo bioequivalence study requirements for its 1 mg and 0.5 mg strengths of the test product, based on the in-vivo bioequivalence study for the 2 mg strength, comparative dissolution data (**Table** 7) and formulations similarly proportional to that of the 2 mg strength (**Table 8**).

COMMENTS:

1. In the in vivo bioequivalence study, the firm has prohibited the study volunteers from ingesting prescription drugs for 1 week and alcohol for 24 hours before study dosing. The Division of Bioequivalence generally prefers that prescription drugs be prohibited for 2 weeks and alcohol for 48 hours before study dosing and the firm is advised to incorporate these restrictions into future protocols.

2. The formulations of the 1 mg and 0.5 mg test product strengths are similarly proportional to that of the 2 mg strength and both the 1 mg and 0.5 mg test products have met the USP/FDA in vitro dissolution requirements.

DEFICIENCIES:

1. The firm's analytical method SOP #2283 has been submitted in an incomplete form. A complete description of the analytical method, including the complete text of SOP #2283, must be submitted to the application as a condition of approval.

2. In the assay validation section of the bioequivalence study, the firm has not provided data to support the stability of the samples and standards under the frozen storage conditions used in the studies for the 82-day period between sample collection (12/10/94) and assay completion (3/2/95). The firm should submit these data for review.

RECOMMENDATIONS:

1. The bioequivalence study #930851, conducted by Eon Labs Manufacturing on its Bumetanide tablets, 2 mg, lot #941102, versus the listed reference product, Bumex® tablets, 2 mg, manufactured by Roche Laboratories has been found incomplete by the Division of Bioequivalence for the reasons stated in the Deficiencies #1 and #2, above. The firm is advised to comply with the recommendations therein.

2. The dissolution testing conducted by the firm on its Bumetanide tablets, 2 mg, 1 mg, and 0.5 mg, is acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml deaerated water at 37C using USP 23 apparatus 2 (Paddle) at 50 rpm. The test product should meet the following specifications:

Not less than (b)4 of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

3. Wavier of the in-vivo bioequivalence study requirements for the firm's bumetanide tablets, 1 mg and 0.5 mg, cannot be granted by the Division of Bioequivalence pending approval of the firm's bumetanide tablets, 2 mg.

4. From the Bioequivalence viewpoint, the firm has met the in-vitro dissolution requirements, but has not met the in-vivo bioequivalence requirements for its ANDA #74-700, and the application is not acceptable.

The firm should be advised of the Comments, Deficiencies, and Recommendations, above.

/S/

Larry A. Ouderkirk
Division of Bioequivalence
Review Branch 1

Date: 12-19-95

Concur: /S/

Chief, Review Branch 1
Division of Bioequivalence

Date: 12/23/95

cc: ANDA 74-700 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-344 (CVishwanathan), HFD-652 (Huang, Ouderkirk), Drug File, Division File

lao/orig x:\new\firmsam\Eon\ltrs&rev\74700sdw.695

TABLE 1 - PRE-STUDY ASSAY VALIDATION

Parameter	Quality Control Samples	Standard Curve Samples
QC or Std. Curve Conc. (ng/mL)	(b)4 - Confidential Business	
Intrabatch Precision (%CV)		
Intrabatch Accuracy (% Actual)		
Interbatch Precision (%CV)		
Interbatch Accuracy (% Actual)		
Linearity		
Linear Range (ng/mL)		
Sensitivity/LOQ (ng/mL)		
%Recovery Bumetanide (n=5) %Recovery Internal Standard (n=15)		
Stability (n=10): @22^{0}C 3 Freeze-Thaw Cycles Autosampler @ 4^{0}C		
Specificity		

TABLE 2 - ASSAY PERFORMANCE FOR STUDY #930851

Parameter	Quality Control Samples	Standard Curve Samples
Test Conc. (ng/mL)	(b)4 - Confidential Business	
Interbatch Precision (%CV)		
Interbatch Accuracy (%Actual)		
Linearity		
Linear Range (ng/mL)		
Sensitivity/LOQ (ng/mL)		
Stability (n=10): @-22^{0}C Stock Sol. @ -22^{0}C in MeOH Stock Sol. @ 4^{0}C in MeOH		
Specificity		

TABLE 3

MEDICAL EVENTS

Subject	Period	Dosing Time/Date	Sign/Symptom	Time after dosing	Duration	Seriousness	Likelihood	Causality	Probability	Report method	Intensity at Onset	Follow-Up: Time after dosing	Follow-Up: Evolution	Follow-Up: Intensity	Action / Comment
Product Code A															
1	2	09:00: 17/12/94	Headache	7.0h	16.0h	NS	E	D	PR	E	M	23.0h	R	N/A	
3	1	09:04: 10/12/94	Pustule on left biceps	11.9h	12.5h	NS	U	O	PO	SP	M	1.0d	R	N/A	
			Undetermined cause.												
22	1	09:42: 10/12/94	Headache (intermittent)	4.3h	3.3d	NS	E	D	PR	E	M	*	I	MO	Headache became temporal - both sides. * Date and time of follow-up not recorded.
												3.5d	R	N/A	
23	1	09:44: 10/12/94	Headache	5.0h	18.3h	NS	E	D	PR	SP	M	6.0h	U	M	None.
												12.0h	D	M	None.
												23.3h	R	N/A	
23	1	09:44: 10/12/94	Abdominal cramps (intermittent)	17.8h	5.7d	NS	U	O	PO	SP	MO	1.2d	U	MO	None.
			Gastroenteritis.												
												6.5d	R	N/A	

TIME UNITS	SERIOUSNESS	LIKELIHOOD	CAUSALITY	PROBABILITY	REPORT METHOD	INTENSITY	EVOLUTION	GENERAL
d=Days	S=Serious	E=Expected	D=Drug	D=Definite	E=Elicited	M=Mild	I=Increased	N/A = Not Applicable
h=Hours	NS=Non-Serious	U=Unexpected	P=Procedure	PR=Probable	SP=Spontaneous	MO=Moderate	U=Unchanged	N/R = Not Recorded
m=Minutes			O=Other	PO=Possible	O=Observed	S=Severe	D=Decreased	
				U=Unlikely			R=Resolved	

A = Eon 1 x 2 mg bumetanide tablet
B = Roche (Bumex) 1 x 2 mg bumetanide tablet

TABLE 3

MEDICAL EVENTS

Subject	Period	Dosing Time/Date	Sign/Symptom	Time after dosing	Duration	Seriousness	Likelihood	Causality	Probability	Report method	Intensity at Onset	Follow-Up: Time after dosing	Follow-Up: Evolution	Follow-Up: Intensity	Follow-Up: Action / Comment
Product Code A															
23	1	09:44: 10/12/94	Loose stool (liquid) (intermittent)	17.8h	5.7d	NS	U	O	PO	SP	MO	1.2d	U	MO	None.
			Gastroenteritis.									3.3d	U	MO	Subject called the Medical Designate.
												6.5d	R	N/A	

TIME UNITS	SERIOUSNESS	LIKELIHOOD	CAUSALITY	PROBABILITY	REPORT METHOD	INTENSITY	EVOLUTION	GENERAL
d=Days	S=Serious	E=Expected	D=Drug	D=Definite	E=Elicited	M=Mild	I=Increased	N/A = Not Applicable
h=Hours	NS=Non-Serious	U=Unexpected	P=Procedure	PR=Probable	SP=Spontaneous	MO=Moderate	U=Unchanged	N/R = Not Recorded
m=Minutes			O=Other	PO=Possible	O=Observed	S=Severe	D=Decreased	
				U=Unlikely			R=Resolved	

A = Eon 1 x 2 mg bumetanide tablet
B = Roche (Bumex) 1 x 2 mg bumetanide tablet

TABLE 3

MEDICAL EVENTS

Subject	Period	Dosing Time/Date	Sign/Symptom	Time after dosing	Duration	Seriousness	Likelihood	Causality	Probability	Report method	Intensity at Onset	Follow-Up: Time after dosing	Follow-Up: Evolution	Follow-Up: Intensity	Follow-Up: Action / Comment
Product Code B															
10	1	09:18: 10/12/94	Nausea	42.0m	5.3h	NS	E	D	PR	E	M	2.5h 6.0h	D R	M N/A	None.
10	1	09:18: 10/12/94	Headache	57.0m	21.8h	NS	E	D	PR	SP	M	6.0h 11.4h 22.7h	D U R	M M N/A	None. None.
20	1	09:38: 10/12/94	Dizziness	3.9h	18.0m	NS	E	D	PR	O	M	4.1h 4.2h	D R	M N/A	BP- 111/68
26	1	09:50: 10/12/94	Headache (intermittent)	8.2h	5.0h	NS	E	D	PR	E	M	13.2h	R	N/A	

TIME UNITS
d=Days
h=Hours
m=Minutes

SERIOUSNESS
S=Serious
NS=Non-Serious

LIKELIHOOD
E=Expected
U=Unexpected

CAUSALITY
D=Drug
P=Procedure
O=Other

PROBABILITY
D=Definite
PR=Probable
PO=Possible
U=Unlikely

REPORT METHOD
E=Elicited
SP=Spontaneous
O=Observed

INTENSITY
M=Mild
MO=Moderate
S=Severe

EVOLUTION
I=Increased
U=Unchanged
D=Decreased
R=Resolved

GENERAL
N/A = Not Applicable
N/R = Not Recorded

A = Eon 1 x 2 mg bumetanide tablet
B = Roche (Bumex) 1 x 2 mg bumetanide tablet

TABLE 4

FASTING SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY #930851

ARITHMETIC MEAN PLASMA CONCENTRATIONS [NG/ML]
VERSUS TIME (CV%) IN 24 SUBJECTS

TIME (HR)	TEST TREATMENT A	REFERENCE TREATMENT B	RATIO (A/B)
0	0.0	0.0	---------
0.25	6.8 (157)	4.6 (90)	1.48
0.5	36.2 (89)	37.7 (70)	0.96
0.75	54.8 (56)	63.4 (46)	0.86
1	60.4 (39)	66.1 (43)	0.91
1.25	59.6 (36)	64.4 (42)	0.93
1.5	57.2 (30)	63.5 (34)	0.90
1.75	51.0 (29)	57.2 (36)	0.89
2	47.5 (30)	50.2 (35)	0.97
2.5	38.6 (34)	41.0 (40)	0.94
3	31.2 (36)	34.1 (47)	0.91
4	17.6 (51)	21.1 (74)	0.83
5	8.9 (47)	10.7 (74)	0.83
6	4.8 (45)	5.4 (65)	0.89
8	1.6 (70)	1.8 (86)	0.89
12	0.05 (469)	0.12 (336)	0.41

Figure 1

Project No. 930851

Mean Plasma Bumetanide Concentrations

(Linear Plot)

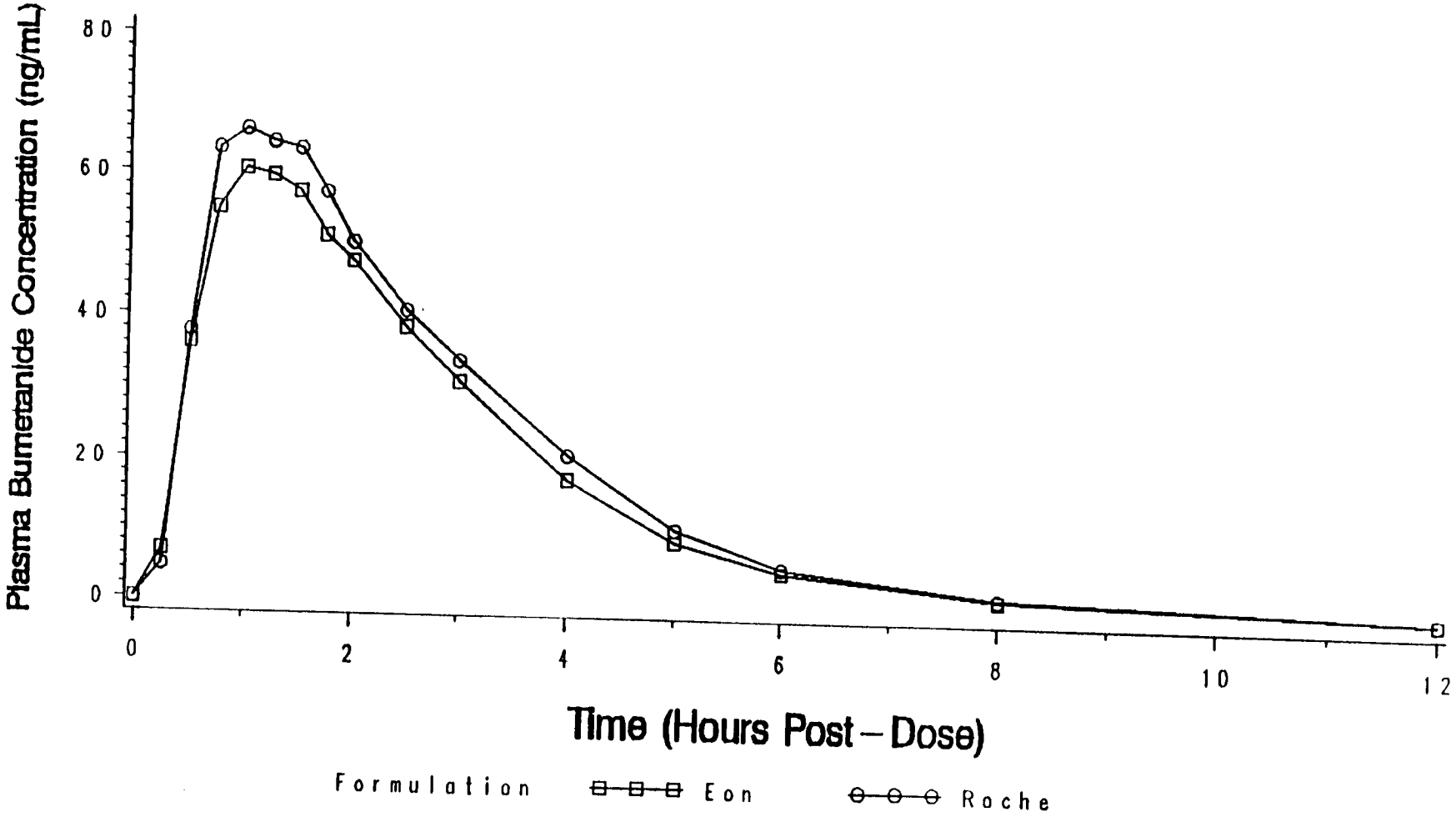

TABLE 5

FASTING SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY #930851

ARITHMETIC MEANS (CV%) OF PHARMACOKINETIC PARAMETERS
FOR BUMETANIDE IN 24 SUBJECTS

PK PARAMETER	N	TEST TREATMENT A	N	REFERENCE TREATMENT B	RATIO (A/B)
AUCT [ng•hr/mL]	24	176.4 (22)	24	196.3 (31)	0.93
ln AUCT [ng•hr/mL]	24	5.1496	24	5.2600	----
(Geometric mean)	24	172.4	24	189.1	0.91
AUCI [ng•hr/mL]	24	180.6 (22)	24	199.7 (30)	0.93
ln AUCI [ng/mL]	24	5.1733	24	4.3563	----
(Geometric mean)	24	176.5	24	192.5	0.92
Cmax [ng/mL]	24	73.5 (31)	24	80.4 (26)	0.94
ln Cmax [ng/mL]	24	4.2549	24	4.3563	----
(Geometric mean)	24	70.4	24	78.0	0.90
Tmax [hr]	24	1.5 (58)	24	1.3 (59)	1.15
K_{el} [1/hr]	24	0.6138 (16)	24	0.6205 (15)	0.99
$T_{1/2}$ [hr]	24	1.156 (15)	24	1.141 (15)	1.01

TABLE 6

FASTING IN VIVO BIOEQUIVALENCE STUDY #930851

LEAST-SQUARES MEANS OF PHARMACOKINETIC PARAMETERS
FOR BUMETANIDE IN 24 SUBJECTS

PK PARAMETER	TEST TREATMENT A	REFERENCE TREATMENT B	RATIO (A/B)	90% C.I.
AUC(T) [ng•hr/mL]	176.4	196.3	0.93	-------
ln AUC(T) [ng•hr/mL]	5.1496	5.2420	-----	-------
(Geometric mean)	172.4	189.1	0.91	85-98
AUC(I) [ng•hr/mL]	180.6	199.7	0.93	-------
ln AUC(I) [mcg•hr/mL]	5.1733	5.2600	-----	-------
(Geometric mean)	176.5	192.5	0.92	85-99
Cmax [ng/mL]	73.5	80.4		-------
ln Cmax [ng/mL]	4.2549	4.3563	-----	-------
(Geometric mean)	70.4	78.0	0.90	82-99
Tmax [hr]	1.5	1.3	1.15	-------
K_{el} [1/hr]	0.6138	0.6205	0.99	-------
$T_{1/2}$ [hr]	1.156	1.141	1.01	-------

Table 7 - In Vitro Dissolution Testing

Drug: Bumetanide
Strength(s): 2 mg, 1 mg, 0.5 mg
ANDA No.: 74-700
Firm: Eon Labs Manufacturing
Submission Date: June 15, 1995
File Name: 74700sdw.695

I. Conditions for Dissolution Testing:

USP 23 Apparatus:	2 (Paddle)	Volume:	900 ml
RPM:	50	Tolerance:	(b)4 - Confidential Business
No. Units Tested:	12	Reference Drug:	
Medium:	Water	Assay Method:	

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot #941102 Strength: 2 mg			Reference Product Lot #0310 Strength: 2 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
10	82.9	(b)4 - Confidential Business	5.6	96.0	(b)4 - Confidential Business	7.3
20	94.3		4.1	101.0		4.3
30	96.9		3.6	101.6		1.1

Test Product USP Content Uniformity (CV%): 99.3% (1.7); USP Assay: 99.5%
Ref. Product USP Content Uniformity (CV%): 104.2% (2.2); USP Assay: 99.4%

Sampling Times (Minutes)	Test Product Lot #941206 Strength: 1 mg			Reference Product Lot #0622 Strength: 1 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
10	69.8	(b)4 - Confidential Business	5.5	98.4	(b)4 - Confidential Business	5.2
20	92.2		3.7	102.9		0.5
30	99.9		1.8	103.4		0.6

Test Product USP Content Uniformity (CV%): 97.8% (1.6); USP Assay: 99.7%

Sampling Times (Minutes)	Test Product Lot #941204 Strength: 0.5 mg			Reference Product Lot #0118 Strength: 0.5 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
10	75.8	(b)4 - Confidential Business	4.2	95.6	(b)4 - Confidential Business	4.6
20	91.1		1.3	99.1		1.6
30	96.6		1.2	99.5		1.9

Test Product USP Content Uniformity (CV%): 100.5% (1.2); USP Assay: 101.7%

TABLE 8

COMPARATIVE FORMULATIONS FOR BUMETANIDE TABLETS MANUFACTURED BY EON LABORATORIES

INGREDIENT	AMOUNT (MG) PER TABLET STRENGTH		
	0.5 MG TABLET	1 MG TABLET	2 MG TABLET
BUMETANIDE, USP	0.5	1.0	2.0
MICROCRYSTALLINE CELLULOSE, NF*	(b)4 - Confidential Business		
ISOPROPYL ALCOHOL, USP			
ANHYDROUS LACTOSE, NF			
MAGNESIUM STEARATE, NF			
CORN STARCH, NF			
PREGELATINIZED STARCH, NF			
TALC, USP			
PURIFIED WATER, USP			
GREEN LAKE BLEND			
D&C YELLOW NO. 10 ALUMINUM LAKE			
IRON OXIDE, BROWN			
TOTAL TABLET WEIGHT	85 mg	170 mg	340 mg

*(Amount may vary slightly to adjust final batch weight).

ANDA 74-700

MAY 23 1996

Eon Labs Manufacturing, Inc.
Attention: Maxine M. Gallagher
227-15 North Conduit Avenue
Laurelton NY 11413

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Bumetanide Tablets USP, 0.5 mg, 1 mg, 2 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be conducted in 900 ml deaerated water at 37°C using USP 23 apparatus 2 (Paddle) at 50 rpm. The test product should meet the following specifications:

   Not less than (b)4 of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 74-700, Original, DUP Jacket
Division File
Field Copy
HFD-600 Reading File
Letter Out, Bio Acceptable

Endorsements:

L. Ouderkirk LaO 5/21/96
Y. C. Huang
J. Gross

DRAFTED: STM 05/21/96 X:\WPFILE\BIO\FINAL\N74700.APP

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

Not post Sensin.

ANDA/AADA # 74-700 SPONSOR: EON Labs Manufacturing
DRUG: Bumetanide
DOSAGE FORM: Tablets
STRENGTH(s): 2.0 mg, 1.0 mg, 0.5 mg
TYPE OF STUDY: (Single)/Multiple (Fasting)/Fed
STUDY SITE: (b)4 - Confidential Business

STUDY SUMMARY: Firm has conducted a fasted, SD, 2-way Crossover study on 24 healthy males. 90% C.I.'s for ln AUC(T) ln AUC(I) and ln Cmax were 85-98%, 85-99%, and 82-99%, respectively, satisfying the in-vivo biostudy requirements. Waiver was granted for 1 mg and 0.5 mg tablet strengths based on acceptable dissolution and proportional formulation to 2 mg strength.

DISSOLUTION: 2mg, 1mg, & 0.5 mg strengths met the USP 23 dissolution requirement of NLT (b)4 - dissolved in 30 minutes

PRIMARY REVIEWER: Larry A. Conforti BRANCH: RBI

INITIAL: /S/ DATE: 5/10/96

BRANCH BRANCH: I

INITIAL: /S/ DATE: 5/16/96

DIRECTO
DIVISION

INITIAL: /S/ DATE: 5/21/96

DIRECTO
OFFICE OF GENERIC DRUGS

INITIAL: N/A DATE:

5/21/96

DBE STUDY APPROVAL FORM

ANDA#: 74-700 **First Generic (Y/N):** (Y)
FIRM: Eon
DRUG/FORM(S)/STRENGTH: Tablets, 2mg, 1mg, 0.5mg
RLD (FIRM): Burnex Tablets (Roche) **BIO-REVIEWER:** L.A. Ouderkirk
TYPE OF STUDY: (SD) 1x20mg SD/fed **MD** **Others:**
Therapeutic Category/Dosage Regimen: Diuretic / 0.5-2.0 mg/Day
Biopharm classification (solubility/permeability): High solubility, high permeability

Clinical Procedure - Center: [redacted] (b)4 - Confidential Business
# of subjects (planned+extra): 24 + 2
# of subjects completed: 25
Subset analysis: None
Randomization: Balanced
Dose administration: 1x 2.0 mg Tablet
Safety Summary:
10 Adverse events 6 - Test 4 - Ref.
(All mild-moderate intensity)
dropped out (reason): 1 - cramping/loose stools
in data analysis (reason): 24 (per protocol)
Demographic: Caucasian males, 18-40 years
Blood sample: All taken within 3 min. of designated time.

Analytical Procedure - Center: [redacted] (b)4 - Investigator: (Same)
Analytical method: [redacted] (b)4 - Confidential
Pre-study validation:
Stability: long (86 days)/short ( )/bench (6.5 Hr)/freeze-thaw cycle (3)
Within-study validation:
Calibration: 1.0 - 195.4 ng/ml
Comments: C.V.% | 1.2 - 11.8 (Intersubject Variability)
% Actual | 93.7 - 104.5
QC samples: 3.0 - 160.0 ng/ml
C.V% | 1.7 - 5.2
% Actual | 94.2 - 113.9

PK/Statistical Analysis - Center: [redacted] (b)4 - Investigator: (Same)
PK Calculation procedure: (Checked C.T.) ✓
Mean plasma profile: Graphs
Indvidual plasma profile: Graphs
Summary of PK parameters:

	Test	Ref	T/R	90% C.I. (24 Subj)	90% CI (22 Subj)
AUCT	176.4	196.3	0.93	85-98	85-99
AUCI	180.6	199.7	0.93	85-99	85-100
Cmax	73.5	80.4	0.94	82-99	80-97

Comments: Low predose levels, BQL = 1

Statistical calculation procedure: SAS GLM
Comments (estimated intra-, inter- and total variabilities):

	Inter (%CV) T	Inter (%CV) R	Intra (% CV)
AUCT	22%	31%	15%
AUCI	22%	30%	15%
Cmax	31%	26%	19%

Good HD 10, 20, 30 min Sorpm >85% @ 20 min.
In Vitro Dissolution/USP specs: NLT [redacted] (b)4 (Q) in 30 minutes (USP 23)
Firm submitted data: 2mg, 1mg, 0.5mg Test Product Vs. Burnex Tablets
Acceptable
Waiver Request - 1mg, 0.5mg Strengths granted Waiver Exactly proportional
Comparison to Past Generic & Reference Products (Zenith) Compares favorably

file:Protocol/fdabiock.wp (version 8/23/95)

Approved 5/21/96

MAY 20 1996

Bumetanide
Tablets, 2.0 mg, 1.0 mg, 0.5 mg
ANDA #74-700
Reviewer: L.A. Ouderkirk
WP #74700sw.296

Eon Labs Manufacturing
Laurelton, New York
Submission Date:
February 21, 1996

Review of an Amended In Vivo Bioequivalence Study and a Waiver Request

REVIEW HISTORY:

The firm has previously submitted a two-way crossover fasted bioequivalence study (#930851) on its bumetanide tablets, 2 mg, versus Bumex® tablets, 2 mg, manufactured by Roche Laboratories (see submission to ANDA #74-700 dated 6/15/95 by L.A. Ouderkirk, Division of Bioequivalence). The study was found incomplete because the firm did not submit a complete description of the analytical method and did not provide data to support the stability of the samples and standards under the frozen storage conditions used in the study for the 82-day period between sample collection (12/10/94) and assay completion (3/2/95).

The firm's request for waiver of the in vivo bioequivalence requirements for the 1 mg and 0.5 mg strengths of the test product was denied pending approval of the in vivo study.

PRESENT SUBMISSION:

The firm has responded to the above referenced deficiency comments as follows:

A. Description of Analytical Method

The firm has submitted a complete description of its analytical method SOP LC-M-2283-00, [redacted]

(b)4 - Confidential Business

B. Long-Term Stability Data

The firm has submitted additional assay validation data for the in vivo bioequivalence study #930851 to support the stability of frozen samples for a period of 86 days at a nominal storage temperature of -22°C (see **Table 1**). The pre-study assay validation data is also given (**Table 2**) for convenience.

COMMENTS:

1. The firm has responded satisfactorily to the Division's request for a complete and unexpurgated description of the assay method used for the in vivo bioequivalence study #930851.

2. The firm has also responded satisfactorily to the Division's request for validation data on the long-term stability of frozen samples stored under the conditions specified in bioequivalence study #930851 (**Table 1**).

3. The formulations of the 1 mg and 0.5 mg test product strengths have previously been found similarly proportional to that of the 2 mg strength (**Table** 3).

4. The 2 mg, 1 mg, and 0.5 mg test product strengths have previously met the USP 23/FDA in vitro dissolution requirements (**Table** 4; see also review of submission to ANDA 74-700 dated June 15, 1995, by L.A. Ouderkirk, Division of Bioequivalence).

5. Plasma concentration versus time data and pharmacokinetic summary data for study #930851 are presented in **Tables** 5-7 for convenience.

RECOMMENDATIONS:

1. The bioequivalence study #930851, conducted by Eon Labs Manufacturing on its Bumetanide Tablets, 2 mg, lot #941102, versus the listed reference product, Bumex® tablets, 2 mg, manufactured by Roche Laboratories, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Eon's Bumetanide Tablets, 2 mg, are bioequivalent to Bumex® tablets, 2 mg.

2. Waiver of the in-vivo bioequivalence study requirements for the firm's 1 mg and 0.5 mg strengths of the test product is granted by the Division of Bioequivalence per 21 CFR 320.22 (d)(2). The formulations of the 1 mg and 0.5 mg test product strengths are similarly proportional to that of the 2 mg strength, which has demonstrated its bioequivalence to a reference product in vivo. The 2 mg, 1 mg, and 0.5 mg test products have met the USP23/FDA in vitro dissolution requirement. The 1 mg and 0.5 mg test products are therefore deemed bioequivalent to the identical strengths of Bumex® tablets, manufactured by Roche Laboratories.

3. From the Bioequivalence viewpoint, the firm has met the in-vivo bioequivalence and in-vitro dissolution requirements, and the ANDA #74-700 is acceptable.

/S/

Larry A. Ouderkirk 5/17/96
Division of Bioequivalence
Review Branch 1

RD INITIALED YCHuang
FT INITIALED YCHuang

/S/ 5/17/96

Concur: /S/ Date: 5/20/96

K[redacted] Ph.D.
D[redacted]sion of Bioequivalence

cc: ANDA 74-700 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-344 (CVishwanathan), HFD-652 (Huang, Ouderkirk), Drug File, Division File

lao/orig x:\new\firmsam\Eon\ltrs&rev\74700sw.296

TABLE 1 - REVISED ASSAY PERFORMANCE FOR STUDY #930851

Parameter	Quality Control Samples	Standard Curve Samples
Test Conc. (ng/mL)	(b)4 - Confidential Business	
Interbatch Precision (%CV)		
Interbatch Accuracy (%Actual)		
Linearity		
Linear Range (ng/mL)		
Sensitivity/LOQ (ng/mL)		
Stability (n=10): @-22°C in plasma Stock Sol. @ -22°C in MeOH Stock Sol. @ 4°C in MeOH		
Specificity		

TABLE 2 - PRE-STUDY ASSAY VALIDATION

Parameter	Quality Control Samples	Standard Curve Samples
QC or Std. Curve Conc. (ng/mL)	(b)4 - Confidential Business	
Intrabatch Precision (%CV)		
Intrabatch Accuracy (% Actual)		
Interbatch Precision (%CV)		
Interbatch Accuracy (% Actual)		
Linearity		
Linear Range (ng/mL)		
Sensitivity/LOQ (ng/mL)		
%Recovery Bumetanide (n=5)		
%Recovery Internal Standard (n=15)		
Stability (n=10): @22°C 3 Freeze-Thaw Cycles Autosampler @ 4°C		
Specificity		

TABLE 3

COMPARATIVE FORMULATIONS FOR BUMETANIDE TABLETS MANUFACTURED BY EON LABORATORIES

INGREDIENT	AMOUNT (MG) PER TABLET STRENGTH		
	0.5 MG TABLET	1 MG TABLET	2 MG TABLET
BUMETANIDE, USP	0.5	1.0	2.0
MICROCRYSTALLINE CELLULOSE, NF*	(b)4 - Confidential Business		
ISOPROPYL ALCOHOL, USP			
ANHYDROUS LACTOSE, NF			
MAGNESIUM STEARATE, NF			
CORN STARCH, NF			
PREGELATINIZED STARCH, NF			
TALC, USP			
PURIFIED WATER, USP			
GREEN LAKE BLEND			
D&C YELLOW NO. 10 ALUMINUM LAKE			
IRON OXIDE, BROWN			
TOTAL TABLET WEIGHT			

*(Amount may vary slightly to adjust final batch weight).

Table 4 - In Vitro Dissolution Testing

Drug: Bumetanide
Strength(s): 2 mg, 1 mg, 0.5 mg
ANDA No.: 74-700
Firm: Eon Labs Manufacturing
Submission Date: June 15, 1995

I. Conditions for Dissolution Testing: (USP 23)

USP 23 Apparatus:	2 (Paddle)	Volume:	900 ml
RPM:	50	Tolerance:	NLT 85% (Q) in 30 min.
No. Units Tested:	12	Reference Drug:	Bumex® Tablets (Roche)
Medium:	Water	Assay Method:	HPLC w/UV abs. @ 254 nm

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot #941102 Strength: 2 mg			Reference Product Lot #0310 Strength: 2 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
10	82.9	(b)4 - Confidential Business	5.6	96.0	(b)4 - Confidential Business	7.3
20	94.3		4.1	101.0		1.3
30	96.9		3.6	101.6		1.1

Test Product USP Content Uniformity (CV%): 99.3% (1.7); USP Assay: 99.5%
Ref. Product USP Content Uniformity (CV%): 104.2% (2.2); USP Assay: 99.4%

Sampling Times (Minutes)	Test Product Lot #941206 Strength: 1 mg			Reference Product Lot #0622 Strength: 1 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
10	69.8	(b)4 - Confidential Business	5.5	98.4	(b)4 - Confidential Business	5.2
20	92.2		3.7	102.9		0.5
30	99.9		1.8	103.4		0.6

Test Product USP Content Uniformity (CV%): 97.8% (1.6); USP Assay: 99.7%

Sampling Times (Minutes)	Test Product Lot #941204 Strength: 0.5 mg			Reference Product Lot #0118 Strength: 0.5 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
10	75.8	(b)4 - Confidential Business	4.2	95.6	(b)4 - Confidential Business	4.6
20	91.1		1.3	99.1		1.6
30	96.6		1.2	99.5		1.9

Test Product USP Content Uniformity (CV%): 100.5% (1.2); USP Assay: 101.7%

TABLE 5

FASTING SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY #930851

ARITHMETIC MEAN PLASMA CONCENTRATIONS [NG/ML]
VERSUS TIME (CV%) IN 24 SUBJECTS

TIME (HR)	TEST TREATMENT A	REFERENCE TREATMENT B	RATIO (A/B)
0	0.0	0.0	---------
0.25	6.8 (157)	4.6 (90)	1.48
0.5	36.2 (89)	37.7 (70)	0.96
0.75	54.8 (56)	63.4 (46)	0.86
1	60.4 (39)	66.1 (43)	0.91
1.25	59.6 (36)	64.4 (42)	0.93
1.5	57.2 (30)	63.5 (34)	0.90
1.75	51.0 (29)	57.2 (36)	0.89
2	47.5 (30)	50.2 (35)	0.97
2.5	38.6 (34)	41.0 (40)	0.94
3	31.2 (36)	34.1 (47)	0.91
4	17.6 (51)	21.1 (74)	0.83
5	8.9 (47)	10.7 (74)	0.83
6	4.8 (45)	5.4 (65)	0.89
8	1.6 (70)	1.8 (86)	0.89
12	0.05 (469)	0.12 (336)	0.41

TABLE 6

FASTING SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY #930851

ARITHMETIC MEANS (CV%) OF PHARMACOKINETIC PARAMETERS
FOR BUMETANIDE IN 24 SUBJECTS

PK PARAMETER	N	TEST TREATMENT A	N	REFERENCE TREATMENT B	RATIO (A/B)
AUCT [ng•hr/mL]	24	176.4 (22)	24	196.3 (31)	0.93
ln AUCT [ng•hr/mL]	24	5.1496	24	5.2420	----
(Geometric mean)	24	172.4	24	189.1	0.91
AUCI [ng•hr/mL]	24	180.6 (22)	24	199.7 (30)	0.93
ln AUCI [ng/mL]	24	5.1733	24	5.2600	----
(Geometric mean)	24	176.5	24	192.5	0.92
Cmax [ng/mL]	24	73.5 (31)	24	80.4 (26)	0.94
ln Cmax [ng/mL]	24	4.2549	24	4.3563	----
(Geometric mean)	24	70.4	24	78.0	0.90
Tmax [hr]	24	1.5 (58)	24	1.3 (59)	1.15
K_{el} [1/hr]	24	0.6138 (16)	24	0.6205 (15)	0.99
$T_{1/2}$ [hr]	24	1.156 (15)	24	1.141 (15)	1.01